REMARKS

Applicant respectfully requests reconsideration. Claims 15-19 were previously pending. Claims 15 and 19 have been amended. Claims 16-18 have been canceled. As a result, claim 15 and 19 are pending. No new matter has been added.

Rejections Under 35 U.S.C. §103

The Examiner maintained the rejection of the claims under 35 U.S.C. §103(a) as being unpatentable over Grimble RF (Effect of Antioxidative Vitamins on Immune Function with Clinical Applications. Internat. J. Vit. Nutr. Res. (1997); 67(5):312-20) (Referred to as "Grimble, et al..") in combination with Grimble, Robert, "Modification of Inflammatory Aspects of Immune Function by Nutrients," Nutrition Research, Vol. 18, No. 7, pages 1297-1317 (1998) (Referred to as "Grimble II").

The Examiner did not find Applicant's previously filed arguments to be persuasive. The Examiner reiterates that "[a]t the time the present invention was disclosed, it was well-known in the art that there is a *direct correlation* between the functionality of balanced cytokine production when reacting to an inflammatory response and the activity of the glutathione production pathway to limit the creation of excessive cytokines (See Grimble II, page 1308, latter portion of Conclusion paragraph 3)[2]." (Emphasis added). The Examiner alleges that "endogenous nutrient provision, i.e., glutathione production, controls *hyperactivity* of cytokines, or hypercytokinemia, and "[v]itamin B6 and riboflavin participate in the maintenance of glutathione status" (see Abstract)." (Emphasis added).

The Examiner also cites Grimble II for teaching that "deficiencies in vitamin E, B_6 and riboflavin reduce cell numbers in lymphoid tissues of experimental animals and produce functional abnormalities in the cell mediated immune response." The Examiner alleges that "where there is a deficiency i[n] riboflavin, endogenous nutrient provision provided by glutathione will lack, thereby creating a heightened immune/inflammatory response that wields the over- or hyper-production of cytokines. Therefore, if a deficiency in riboflavin contributes to a heightened inflammatory response then it logically flows mechanistically that the presence of riboflavin has an inverse relationship with cytokine production as an immune response."

According to the Examiner, "[i]t is the establishment of this relationship that makes the prior art rejection in Grimble et al. applicable to the instant invention."

The Examiner also alleges that Grimble et al. teaches that "antioxidative vitamins *such as riboflavin* prevent increased cytokine production *via the glutathione production pathway*." (Emphasis added). According to the Examiner, "one of ordinary skill in the art would have found it obvious that a reduction in cytokines would be efficacious in the treatment of hypercytokinemia."

The Examiner also alleges that "[t]he use of a salt of riboflavin would have been obvious to one of ordinary skill in the art since salts dissociate and a salt of riboflavin would naturally dissociate into riboflavin and the salt." The Examiner further asserts that "to treat a patient, one would need to administer the riboflavin and such as claimed in claim 19 would have been obvious to one of ordinary skill in the art." The Examiner concludes that Grimble "teaches and makes *prima facie* obvious how to use the claimed invention at the time that it was made."

Applicant respectfully disagrees and traverses the rejection. Contrary to the Examiner's assertions, the Grimble references, alone or in combination, do not teach or sugget that "glutathione production, controls hyperactivity of cytokines, or hypercytokinemia" nor do they "establish" an "inverse relationship" between the presence of riboflavin and cytokine production.

The antioxidant vitamins taught by Grimble et al. to prevent increased cytokine production are ascorbic acid and the tocopherols. Neither of the Grimble references teaches or suggests that riboflavin prevents increased cytokine production via the glutathione production pathway (or otherwise) as asserted by the Examiner.

The "Summary" in Grimble et al. recites (Emphasis added):

> "*The antioxidative vitamins, ascorbic acid and the tocopherols, are important* not only for limiting tissue damage but also *in preventing increased cytokine production* which is a consequence of excessive activation of NFκB.....
> Two vitamins, *vitamin B_6 and riboflavin participate in the maintenance of glutathione status.* The former vitamin acts as a cofactor in the synthesis of cysteine (the rate limiting precursor for glutathione biosynthesis) and the latter vitamin is a cofactor for glutathione synthetase. *Deficiencies in tocopherol, vitamin B_6 and riboflavin reduce cell numbers in lymphoid tissues of experimental*

animals and produce functional abnormalities in the cell mediated immune response."

Also, the "Conclusion" in Grimble et al. teaches (Emphasis added):

"The interaction between the response of the immune system to pathogens and inflammatory agents, and antioxidative vitamins is complex. However two common themes emerge amid the complexity (Fig. 4).

The first of these is the influence of antioxidant defense upon the immune response. Inflammatory aspects of the response will be changed in their intensity by the extent of release of inflammatory mediators into extracellular compartments of the body and by the extent of activation of transcription factors, such as NFκB, at the intracellular level. Poor antioxidant defenses, or enhanced antioxidant production, will increase the intensity of these events and hence the extent of the inflammatory response. *Increased intakes of vitamin C and E will counteract this effect.*

The second of the themes may relate to intracellular glutathione concentrations. The molecule acting in its role as an antioxidant and as a modulator of the interaction between NFκB and DNA within lymphocytes and other cells. *Likewise vitamins which have no direct antioxidative properties but which influence glutathione metabolism, may exert a modulatory role. Such vitamins are riboflavin, which is an important co-factor for glutathione reductase* and vitamin B_6 which is important in the synthetic pathway for cysteine, the rate limiting precursor for glutathione synthesis."

The above text clearly teaches that vitamin C (ascorbic acid) and vitamin E (tocopherol) are the vitamins important in preventing increased cytokine production and that riboflavin may exert a modulatory role on the inflammatory response by acting as a cofactor for glutathione reductase. There is no teaching or suggestion in the above that that riboflavin decreases cytokine production.

Applicant has reviewed the Grimble references and, contrary to the Examiner's assertion, did not find any teaching or suggestion in the entire references that riboflavin prevents increased cytokine production as alleged by the Examiner. In fact, Grimble teaches that role of riboflavin on immune function is "unclear". The role of riboflavin as taught by the Grimbles references is summarized in Grimble et al., on page 317 left column, 2nd full paragraph:

> "[r]iboflavin is an important cofactor in glutathione metabolism because of its role as a cofactor for glutathione reductase. However, whether this role is responsible for the influence of the vitamin on immune function is unclear."

The only examples in the Grimble references of the effects of a lack of riboflavin are: a decrease in lymphocytes, decreased thymus weight, and a decreased antibody response. Thus, the Grimble references do not teach or suggest a relationship between riboflavin and cytokine production via the glutathione production pathway as alleged by the Examiner.

Therefore, the teachings of the Grimble references do not provide any reason for one of ordinary skill in the art to use riboflavin to reduce cytokines or to use riboflavin to treat hypercytokinemia, let alone have a reasonable expectation of success in doing so.

Furthermore, Applicant tested the effect of vitamin B2 (riboflavin sodium phosphate) on glutathione levels in mice and rat erythrocytes and found that vitamin B2 had no effect on glutathione levels in erythrocytes in LPS (lipopolysaccharide)-treated rats and mice. These results indicate that riboflavin does not prevent increased cytokine production via the glutathione production pathway. Applicant, herewith, submits a Declaration under 37 C.F.R. § 1.132 describing the experimental conditions and data.

The only way to arrive at the Examiner's conclusion is through the application of hindsight reconstruction of Applicant's invention based on the teachings in Applicant's specification. This is improper. Applicant notes that "it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art." In re Wesslau, 353 F.2d 238, 241, 147 USPQ 391, 393 (CCPA 1965); see also In re Mercer, 515 F.2d 1161, 1165-66, 185 USPQ 774, 778 (CCPA 1975); In re Geiger, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987).

As to the Examiner's allegation that the use of a salt of riboflavin would have been obvious to one of ordinary skill in the art since salts dissociate and a salt of riboflavin would naturally dissociate into riboflavin and the salt, Applicant, without conceding to the correctness of the Examiner's position and in order to advance prosecution, amended claims 15 and 19 and canceled claims 16-18.

In view of the above arguments, withdrawal of the rejection of the claims under 35 U.S.C. §103, is respectfully requested.

Double Patenting Rejection

The Examiner maintained the provisional rejection of claims 15-19 under the judicially created doctrine of obviousness-type double patenting over claim 1-20 of co-pending US application 10/472621.

Without conceding to the merits of the Examiner's position, Applicants defer substantive rebuttal until the conflicting claims of the above-identified co-pending applications have been allowed.

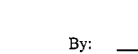
If the provisional double patenting rejection is the only rejection remaining, the Examiner is kindly requested to withdraw the rejection in the instant application and permit the application to issue as a patent (see MPEP § 804).

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is kindly requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Araki et al., Applicant

By: 

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